GLANDULAR LESIONS – PITFALLS IN MANAGEMENT

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Introduction

• Cervical glandular lesions are much less common than squamous lesion
• Incidence increasing, particularly in young women
  • Invasive adenocarcinoma accounted for only 5% of cervical cancer cases in 1950s and 1960s
  • Increased to 20-25%
  • Up to 30% in young women < 35 yrs of age
• Adenocarcinoma-in-situ (AIS)
  • Precursor of invasive adenocarcinoma
  • Age range 18-75 yrs, mean 35-38.8 yrs
    • AIS 15 yrs younger than adenocarcinoma
  • Incidence ratio of AIS to CIN 3 reported as 1:26 to 1:237
• Mixed disease
  • 46%-72% AIS or invasive adenocarcinoma coexist with squamous lesion
Challenges in Management of Cervical Glandular Abnormalities

- **Screening**
  - Cytology less sensitive in detecting glandular dysplasia

- **Diagnosis**
  - Colposcopic features of AIS / adenocarcinoma subtle and non-specific

- **Choice of diagnostic excisional procedures**
  - Cold knife conization vs Loop excision (LEEP)
  - Achieve negative margins

- **Management of AIS after diagnostic excisional procedure**
  - Hysterectomy vs Conservative treatment when future fertility is desired

- **Surveillance protocol for patient opted for conservative management**

- **Endocervical versus endometrial origin of adenocarcinoma**
Screening - Cytology

- 2014 Bethesda Nomenclature for Glandular Abnormalities
  - Atypical
    - Endocervical cells (NOS or specify in comments)
    - Endometrial cells (NOS or specify in comments)
    - Glandular cells (NOS or specify in comments)
  - Atypical
    - Endocervical cells, favor neoplastic
    - Glandular cells, favor neoplastic
  - Endocervical adenocarcinoma in situ
  - Adenocarcinoma
    - Endocervical
    - Endometrial
    - Extrauterine
    - Not otherwise specified (NOS)
Screening - Cytology

- Cervical cytology is generally less sensitive in detecting glandular abnormalities compared to squamous lesions
  - Differentiate high-grade squamous cells vs glandular cells
  - Mimickers: endometrial cells, reactive endocervical cells, tubal metaplasia, cervical endometriosis
- Cytology results just prior to diagnosis of AIS:
  - Glandular – Only 38%-69%
  - Squamous – 26-31%
  - Mixed squamous and glandular – 15%
  - Negative – 4%
- Most glandular lesions are recognized in the course of the evaluation of women with abnormal squamous cytology
- 60% AIS buried under normal metaplastic or dysplastic squamous epithelium making the glandular component inaccessible to cytological sampling
Atypical Glandular Cells (AGC)

- < 0.5% of all cervical cytology
- ~50% coexist with squamous cytological abnormality (ASC / SIL)
- ~30% associated with premalignant or malignant disease
- Not specific to glandular cervical neoplasia
## Possible Histological Diagnosis after AGC

<table>
<thead>
<tr>
<th>Histology</th>
<th>Rates</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous Intraepithelial Lesions (SIL)</td>
<td>20-28%</td>
<td>• Most are squamous (high-grade) rather than glandular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Coexist with glandular lesions</td>
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<tr>
<td>Low-grade CIN 1</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>High-grade CIN 2-3</td>
<td>11%</td>
<td></td>
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<tr>
<td>SCC</td>
<td>0.3-1%</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma-in-situ (AIS)</td>
<td>3-4%</td>
<td>• ~50% coexist with CIN</td>
</tr>
<tr>
<td>Cervical Adenocarcinoma</td>
<td>1-2%</td>
<td></td>
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<tr>
<td>Endometrial Hyperplasia</td>
<td>1%</td>
<td></td>
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<tr>
<td>Endometrial Carcinoma</td>
<td>2-3%</td>
<td></td>
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<tr>
<td>Ovarian Cancer</td>
<td>0.1-0.6%</td>
<td>• Others: fallopian tubes, metastatic (e.g. colon, breast)</td>
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<tr>
<td>Benign</td>
<td>64-71%</td>
<td>• Reactive or reparative changes</td>
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<tr>
<td></td>
<td></td>
<td>• Cervical polyps</td>
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<tr>
<td></td>
<td></td>
<td>• Microglandular hyperplasia associated with OCPs</td>
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<tr>
<td></td>
<td></td>
<td>• Endocervical changes associated with IUD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tubal metaplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cervical endometriosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Arias-Stella reaction (pregnancy change)</td>
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</tbody>
</table>

Significance of AGC

- Risk of neoplasia is higher when reported as “AGC favor neoplasia” or “Endocervical AIS”

<table>
<thead>
<tr>
<th>Subcategories</th>
<th>Risks</th>
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<tbody>
<tr>
<td>AGC-NOS</td>
<td>• 9%-41% invasive cancer, AIS or CIN 2-3</td>
</tr>
<tr>
<td>AGC-favor neoplasia</td>
<td>• 27-96% invasive cancer, AIS or CIN 2-3</td>
</tr>
<tr>
<td>Endocervical AIS</td>
<td>• 48-68% AIS</td>
</tr>
<tr>
<td></td>
<td>• 38% invasive cervical adenocarcinoma</td>
</tr>
<tr>
<td>Atypical endometrial cells</td>
<td>• More than 1/3 have significant uterine disease</td>
</tr>
<tr>
<td></td>
<td>• 80% endometrial origin in post-menopausal women</td>
</tr>
<tr>
<td></td>
<td>• 13-18% endometrial cancer</td>
</tr>
<tr>
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<td>• 6-7% high grade lesions and squamous carcinoma</td>
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</table>

- Risk of malignancy with ACG increase with age
  - <40 yrs – 2% (mostly cervical)
  - 40-49 yrs – 2.8%
  - >50 years – 15% (predominant endometrial carcinoma)

Management of Abnormal Glandular Cytology (AGC or AIS)

- Triage by reflex HPV testing is not recommended
  - Although cervical adenocarcinoma is HPV related, endometrial cancer is not, so reflex HPV testing does not identify a subgroup of women who need less invasive assessment
- Triage using repeat cervical cytology is unacceptable
Early Diagnosis of AIS – A Challenge

- Unreliable cytology
- Unreliable colposcopy
  - Colposcopic features of AIS more subtle than CIN and difficult to differentiate from metaplasia or other mimickers (require histology)
- Disease buried underneath normal or dysplastic squamous epithelium
- Small lesion size
  - 48% only involve one quadrant of the cervix
- Skip (multifocal) lesions in 13%-17%
Colposcopic Features of Glandular Lesions - Pitfalls

- No single appearance characterizes glandular lesions (AIS or adenocarcinoma) – non-specific
- Generally accepted colposcopic criteria for grading squamous lesions do not apply to glandular lesions
  - Squamous lesions - Vascular pattern, inter-capillary distance, surface contour, colour tone, demarcations
  - Glandular lesions - The degree of acetowhiteness reflects the degree of villous fusion (the more fusion, the whiter the lesion) and the histologic pseudostratification of columnar cells with their enlarged hyperchromatic nuclei
- Features of AIS overlap with squamous lesions, immature squamous metaplasia and other mimickers
- When glandular and squamous lesions co-exist (46-72%), the squamous component (80% high-grade) is more likely to be visible colposcopically
Three Common Colposcopic Appearance of Glandular Disease

• Papillary expression resembling an immature transformation zone
  • Fused papillae in discrete AW patches, varying in size
  • Look like fused villous processes of early, normal metaplasia
• Flat, variegated red and white area resembling an immature transformation zone (rather than uniform dense AW in high-grade squamous lesions)
• One or more isolated, elevated, individual, densely AW lesions overlying columnar epithelium
Papillary Expression

Individual or fused villi / papillae in discrete AW patches, varying in size

Abnormal papillary coalescence
Prominent atypical vessels, particularly associated with early invasion
Papillary Expression - Mimickers

- Glandular disease vs squamous metaplasia
  - Fusion / coalescence of villi in both squamous metaplasia and AIS
  - Surface distribution of normal metaplastic epithelium and AIS are similar
  - Vessels of central villous core appear as dots when viewed end on
- Fusion of villi does not occur in CIN
Papillary Expression – Epithelial Budding

Fused AW papillae

Look like fused villous processes of early, normal metaplasia
Papillary Proliferations - Mimickers

**Adenocarcinoma**

- Fusion of villi

**Condyloma Acuminata (Wart)**

- Fine and finger-like papillae

- Each papillae has central capillary loop of afferent and efferent blood vessel – single or multiple dots in the tips
- Multiple warty lesions in genital tract

F68 Atypical endocervical cells NOS
Papillary Proliferations - Mimickers

**Adenocarcinoma**

- F68 Atypical endocervical cells NOS
- Fusion of villi
- Necrosis

**Condyloma Acuminata (Wart)**

- F45 LSIL
- F27 LSIL
Flat, Variegated Red and White area

AIS / Adenocarcinoma

Fused papillae

AIS

CIN - Uniform Dense AW
One or More Isolated Densely AW Lesions Overlying Columnar Epithelium

AIS

Columnar epithelium

Coalescence of papillae

F28 Atypical endocervical cells NOS, ASCUS

AIS

Variegated red and white

F40 AGC

Columnar epithelium
Large “Gland” or Crypt Openings

- Associated with excessive mucus, together with other abnormal colposcopic features

Variegated red and white

Large “gland” or crypt openings
Mixed Disease

The presence of two or more squamous lesions separated by glandular-appearing epithelium is highly suggestive of a glandular lesion.

Primary (i.e. not post treatment) squamous lesions do not “skip”, they are always contiguous.
Mixed Disease

F45 Cytology – AGC, favor neoplasia

Mosaic pattern
Biopsy – CIN

Endocervical sampling -
• AIS
• Endocervical adenocarcinoma
• CIN 3

Fused AW villi
Vascular Patterns

Punctuation, mosaic pattern, corkscrew vessels although common in squamous lesions, do not appear in glandular disease.

Central core vessels entrapped within dysplastic squamous epithelium.
Vascular Patterns

Single or multiple dot formations as seen in the tips of the papillary projections

Formed by vessels that course through the villous projections and bend sharply in their tips
Atypical Vessels – Squamous Cell Carcinoma

Corkscrew-like vessels

Waste-thread-like vessels
(dropping a piece of thread on the floor)

Tendril-like vessels
(climbing plants that reach for and then spiral around surrounding structures)
Atypical Vessels – Adenocarcinoma

Waste-thread-like vessels
(dropping a piece of thread on the floor)

Tendril-like vessels
(climbing plants that reach for and then spiral around surrounding structures)

*Character-like vessels

*Root-like vessels
(tapering or bulging)
However, features of AIS can be very subtle
F47 Cytology HSIL
Biopsy Adenocarcinoma
Role of Colposcopy

- Despite the limitations, colposcopy is still important for the following reasons:
  - To exclude clinically overt invasive carcinoma
  - To assess transformation zone (TZ), the extent of the lesion, including any co-existing squamous disease, and obtain biopsy to guide treatment
  - Biopsy is required in all cases to confirm the diagnosis
Management after Colposcopy

Subsequent management depends on:
Initial cytology, colposcopy and biopsy results

- Biopsy Invasive Cancer
  - Manage Accordingly

- Biopsy AIS
  - Diagnostic Excisional Procedure*

- Initial cytology “AGC-favor neoplasia” or “Endocervical AIS”
  - Biopsy: No significant pathology

- Initial cytology “AGC NOS”
  - Follow Up Cytology / Cotest
Diagnostic Excisional Procedure

• Required in all women with AIS / suspected AIS before making any subsequent management decisions:
  • To exclude adenocarcinoma
    • Still ~1% risk of adenocarcinoma for negative margins

• Aim to achieve an interpretable negative margin
  • Positive margin is associated with high risk of residual / persistent disease and recurrence, even adenocarcinoma
  • Should be cylindrical and deep enough to account for the extent of the lesion, depth of crypt involvement and long enough to encompass the length of the disease
  • Avoid thermal injury / distortion to the specimen especially the apex

• Further management decisions based on a thorough histological assessment, especially margin status
Importance of Margins Status

- Meta-analysis evaluating predictive value of conization margin status (n=1278, 33 studies)
- Cold knife cone (CKC), LEEP or laser conization
- Overall 34.4% margins positive

<table>
<thead>
<tr>
<th>Post-Conization</th>
<th>Positive Margins</th>
<th>Negative Margins</th>
<th>Overall</th>
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<tbody>
<tr>
<td></td>
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<td></td>
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<tr>
<td>Patients underwent secondary excision (Re-Cone/Hysterectomy), n=607</td>
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</tr>
<tr>
<td>Residual AIS</td>
<td>52.8% (180/341)</td>
<td>20.3% (54/266)</td>
<td>38.6% (234/607)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>5% (17/341)</td>
<td>1.5% (4/266)</td>
<td>3.5% (21/607)</td>
</tr>
<tr>
<td>Patients treated conservatively, n=671</td>
<td></td>
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<tr>
<td>Recurrence AIS</td>
<td>19.4% (19/98)</td>
<td>2.6% (15/573)</td>
<td>5.1% (34/671)</td>
</tr>
<tr>
<td>Subsequent Adenocarcinoma</td>
<td>6.1% (6/98)</td>
<td>0.3% (2/573)</td>
<td>1.2% (8/671)</td>
</tr>
<tr>
<td>Overall, n=1278</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>5.2% (23/439)</td>
<td>0.7% (6/839)</td>
<td>2.3% (29/1278)</td>
</tr>
</tbody>
</table>
Extent of Excision - Individualized

- Tailored according to the colposcopic findings, age of the patient and childbearing requirements
- For young women, colposcopically visible SCJ
  - More limited excision of the endocervix (i.e. 1cm above SCJ) may be reasonable in women aged less than 36 years
  - Unlikely to have disease extending more than 10 mm from the SCJ
- For older women, or where the SCJ is not visible at colposcopy
  - A cylindrical biopsy should be taken that includes all of the visible TZ and 20mm to 25mm of the endocervical canal
  - Proximal linear extent of AIS may be as far as 25 mm from the SCJ
- Avoid thermal artefact to improve margins assessment
Choice of Diagnostic Excisional Procedures

- Margin status and interpretation of margins are critical to future treatment planning especially in patients wishing to preserve fertility

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Cold Knife Cone (CKC) | • Obtained in one piece  
                          | • Larger depth and width                                                       |
| LEEP                 | • Obtained in several pieces  
                          | • Thermal artifact at the edges obscuring assessment  
                          | • The mucus in glandular mucosa provides less resistance to electric current |
| Laser Conization     | • Size comparable to CKC but also results in thermal artefacts  
                          | • Specialized training and equipment                                           |
Cold Knife Cone (CKC) or LEEP?

- Most retrospective cohort studies have shown that CKC to be superior to LEEP in achieving negative margins in AIS
  - CKC - 17%-25% positive margins
  - LEEP - 20-40% positive margins
- Meta-analysis by Salani et al 2009
  - Of the 14 studies reporting the type of excisional procedure used, 9 (64.3%) reported that CKC resulted in a higher rate of negative margins than LEEP and improved or equivalent rates over laser conization

Cold Knife Cone (CKC) or LEEP?

- Cold knife cone (CKC) was considered the ‘gold standard’
- Up to 50% AIS are diagnosed after loop excision
- Subsequent management controversial – proceed to cold-knife cone regardless of margin
- However, conventional management by CKC has been challenged:
  - Historically, AIS is thought to be a lesion of the endocervical canal with ‘skip’-lesions. However:
    - Multifocal disease is found in only 13%–17% of cases
    - The lesion is usually unicentric, contiguous with the SCJ, and extends up the canal for a variable distance
  - Recent data suggest similar risk of positive margins and oncological outcome after CKC or LEEP
- Advantages of LEEP over CKC
  - Avoidance of general anaesthesia
  - Treatment in outpatient setting
  - Lower morbidity
  - Reduce obstetric complications (2nd trimester miscarriage and preterm delivery), especially for young patients wishing to preserve fertility
Cold Knife Cone (CKC) or LEEP?

- Most are retrospective studies
- Selection bias
- Prospective study is required to determine the oncological outcome and safety

<table>
<thead>
<tr>
<th>Study</th>
<th>LEEP vs CKC</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latif et al 2015, n=115</td>
<td>• Positive margins (20% vs 17%)</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>• Invasive cancer (3.3% vs 4.2%)</td>
<td>Use of larger loop when AIS is known</td>
</tr>
<tr>
<td></td>
<td>• Recurrence of AIS (6.7% vs 8.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Subsequent adenocarcinoma (0 vs 2.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mean specimen volume (3.0 vs 4.3cm³)</td>
<td></td>
</tr>
<tr>
<td>Munro et al 2015, n=338</td>
<td>• Positive margins (31.8% vs 25.5%)</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>• ACIS persistence and/or recurrence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Specimen depth</td>
<td></td>
</tr>
<tr>
<td>Hanegem et al 2012, aged &lt;30, n= 112</td>
<td>• Positive margins (27% vs 21%)</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>• Residual disease (21.4% vs 27.3%)</td>
<td>Clinicians tends to treat smaller lesion with LEEP, larger lesions by CKC</td>
</tr>
<tr>
<td></td>
<td>• Recurrent (0%)</td>
<td></td>
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Guidelines

- ASCCP Guidelines
  - 2001 –
    - Cold-knife cone favored over loop excision
  - 2012 –
    - Diagnostic excision using any modality, but care must be taken to:
      - Keep specimen intact and margins interpretable
      - Avoid fragmentation, including “top-hat” serial endocervical excisions
      - May require larger loops

- British NHS Cervical Screening Program 2016
  - Excisional Procedure ….. individualized……age and colposcopic findings

- Australian Cervical Screening Program 2005
  - Cold-knife cone biopsy should be considered the “gold standard”

- HKCOG 2016
  - Cold-knife cone is recommended
Management of AIS after Diagnostic Excisional Procedure

- Total hysterectomy - treatment of choice for women who have completed childbearing
- Unable to predict the risk of residual disease or recurrence using the same conventional clinicopathological features for squamous lesions:
  - Colposcopic changes associated with AIS can be minimal, so determining the limits of a lesion can be difficult
  - AIS frequently extends into the endocervical canal, complicating determination of the desired depth of excision
  - AIS can be multifocal and discontinuous, so negative margins on an excision specimen do not provide assurance

<table>
<thead>
<tr>
<th>Post Excisional Procedure</th>
<th>Positive Margins</th>
<th>Negative Margins</th>
</tr>
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<tbody>
<tr>
<td>Residual AIS</td>
<td>52.8%</td>
<td>20.3%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>5.2%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

- Difficulties of reliable cytological follow up

Conservative Fertility Sparing Management

• Mean age of AIS 35-38.8 yrs
• Acceptable option - understands that up to 20% residual disease and small risk of cancer (0.7%) even if excision margins are negative
• Re-excision is indicated for positive margins
  • Up to 60% residual disease
  • ~6% invasive disease
• Conservative management for patients with positive excisional margins who decline re-excision should be undertaken with caution
• Require close follow-up even if margins negative
  • Surveillance
    • Negative HPV test after treatment identifies women at low risk for persistent or recurrent AIS
  • Compliance to follow up
Follow Up - HPV DNA Testing

- The safety of conservative management of AIS depends on the accuracy of screening method utilized in predicting the residual disease.
- High-risk HPV DNA was detected in 93% cervical adenocarcinoma (mostly HPV 16/18)
  - HPV 16 most frequent (South East Asia – HPV 18 predominant)
  - HPV 18 more prevalent in adenocarcinoma (39%) than squamous cell carcinoma (18%)
- Combination of cytology and HPV test advantage over cytology alone for early detection of patients at increased risk of recurrence and progression.

Follow Up - HPV DNA Testing

- Costa et al 2007, n=42, margins clear = 21, mean FU 40 months
  - AIS underwent conservative treatment (CKC / LEEP / LASER Cone)
  - FU using colposcopy, PAP smear, ECC +/- biopsy and HPV testing (HC II) repeated at 6-monthly interval
  - HPV testing significantly predicted disease persistence / clearance at the 1st FU visit with OR 12.6 (1.18-133.89)
  - Predictive power of PAP smear (OR 3.3-5.6) did not reach statistical significance at any of the FU visits
  - Combination of PAP smear and HPV testing:
    - NPV of 100% seems to be very useful in prevent unnecessary hysterectomies

<table>
<thead>
<tr>
<th>PAP + HPV Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st FU (at 6 month)</td>
<td>90%</td>
<td>50%</td>
<td>52.9%</td>
<td>88.9%</td>
</tr>
<tr>
<td>2nd FU (at 12 month)</td>
<td>100%</td>
<td>52.6%</td>
<td>40%</td>
<td>100%</td>
</tr>
</tbody>
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Management Algorithm for AIS after Diagnostic Excisional Procedure

Completed childbearing

Future fertility is desired

Margins involved or ECC positive for CIN or AIS

Re-excision to achieve complete excision (preferred)

Margins Negative

Declined re-excision

6 / 12 / 18 months Cytology / Cotesting +/- Colposcopy

Long Term Follow Up / Hysterectomy

Hysterectomy is preferred

ASCCP 2012
NHS Cervical Screening Program 2016
Don’t forget to exclude pelvic pathology if no lesion identified

AGC

AGC-Endometrial Cells

Endometrial Sampling

Positive

Refer for Treatment (if a local excisional procedure is indicated and the original cytology is AGC favour neoplasia, a cold knife cone is recommended)

Negative

All Subcategories (except AGC endometrial cells)

Colposcopy + Biopsy + Endocervical Sampling

Lesion Identified

Endometrial Sampling if not already performed

No Lesion

AGC

Diagnostic Excisional Conization

Ultrasound pelvis to exclude adnexal pathology

No Lesion

Normal Screening

Repeat cytology 6 monthly

4 consecutive normal cytology

Abnormal cytology

Endocervical AIS

AGC NOS

Endometrial Sampling if not already performed

No lesion

AGC favour neoplasia
Pitfalls in the Diagnosis of Invasive Adenocarcinoma in Cervical Biopsy

- Non-cervical adenocarcinoma, especially endometrial cancer with cervical involvement
- Share similar histologic types
- Clinical presentation and imaging is important
- Histologic clues to the origin include:
  - AIS / CIN - favours endocervical origin
  - Endometrial hyperplasia - endometrial origin
- Immunohistochemistry
Endocervical vs Endometrial Adenocarcinoma with Cervical Involvement

- Immunohistochemistry

<table>
<thead>
<tr>
<th></th>
<th>Endocervical Adenocarcinoma</th>
<th>Endometrial Adenocarcinoma with Cervical Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>p16</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>ISH HPV</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CEA</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>ER / PR</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Vimentin</td>
<td>-</td>
<td>+</td>
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</tbody>
</table>

- Pitfalls:
  - ER & PR can vary in both
  - p16 useful, however:
    - p16 also strongly and diffusely positive in high grade serous, some undifferentiated and high grade endometrioid adenocarcinoma
    - p53 diffusely positive in high-grade endometrial adenocarcinomas and metastatic high-grade tubal or ovarian adenocarcinomas involving the cervix, while primary cervical neoplasm should only show weak and heterogeneous staining
  - ISH HPV can be negative in unusual endocervical adenocarcinoma e.g. clear cell, minimal deviation adenocarcinoma, serous, MMMT
Conclusion

- Cytology is less sensitive in detecting glandular dysplasia
- Colposcopic features of AIS / adenocarcinoma is subtle and non-specific
- Diagnostic excisional biopsy should be performed when AIS is found on punch biopsy or suspected cytologically to exclude adenocarcinoma
- Should achieve an interpretable negative margin
- High risk of residual disease and carcinoma if margins positive
- Hysterectomy is the treatment of choice for AIS who have completed childbearing
  - Because of risk of residual disease and occult carcinoma even if excisional margins are clear
- Conservative management is an option when future fertility is desired
  - Understood the possibility of persistent / recurrent disease and small chance of adenocarcinoma even if excisional margins are clear
  - Good compliance to follow up
- Don’t forget to exclude other pelvic malignancy if no lesion is found
- Differentiate between endocervical adenocarcinoma and endometrial adenocarcinoma with cervical involvement
Thank You